# Single-Cell Transcriptomics Reveals Sex-Specific Changes in Cell Death Pathways in Alzheimer's Disease

Luxembourg Centre for System Biomedicine

Mohamed Soudy[1], Sophie Le Bars[1], Enrico Glaab[1]

*1 Biomedical Data Science Group, Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg*

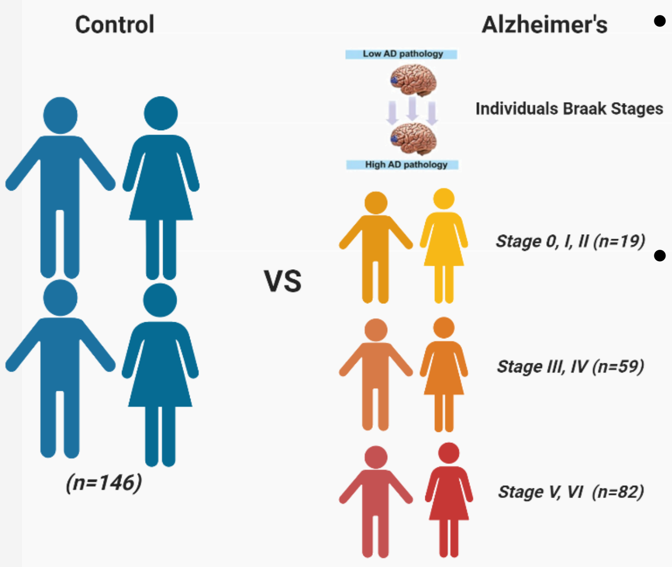
## Abstract

- Alzheimer's disease exhibits significant sex differences in prevalence, progression, and clinical manifestations, but the underlying molecular mechanisms remain unclear.
- We conducted systems-level bioinformatics analyses on a large-scale single-cell transcriptomic atlas of AD, derived from 427 human prefrontal cortex at the systems level samples with varying AD pathology.
- Male astrocytes showed sex-specific modulation of **cell death pathways** involving regulatory genes such as *SGK3* and *ERBB4*, while female astrocytes displayed changes in **Wnt signaling** and **cell cycle pathways.**
- The gene ***RPTOR*** was identified as a key male-specific regulator in astrocytes, with a role in modulating sex-dependent expression changes in AD.

## Background

- AD displays striking heterogeneity in prevalence, progression, and clinical manifestation between the sexes, with women bearing a disproportionate burden of the disease. [1]
- Accumulating evidence from epidemiologic, clinical, and biological studies underscores the importance of understanding these sex differences in AD. [2, 3]

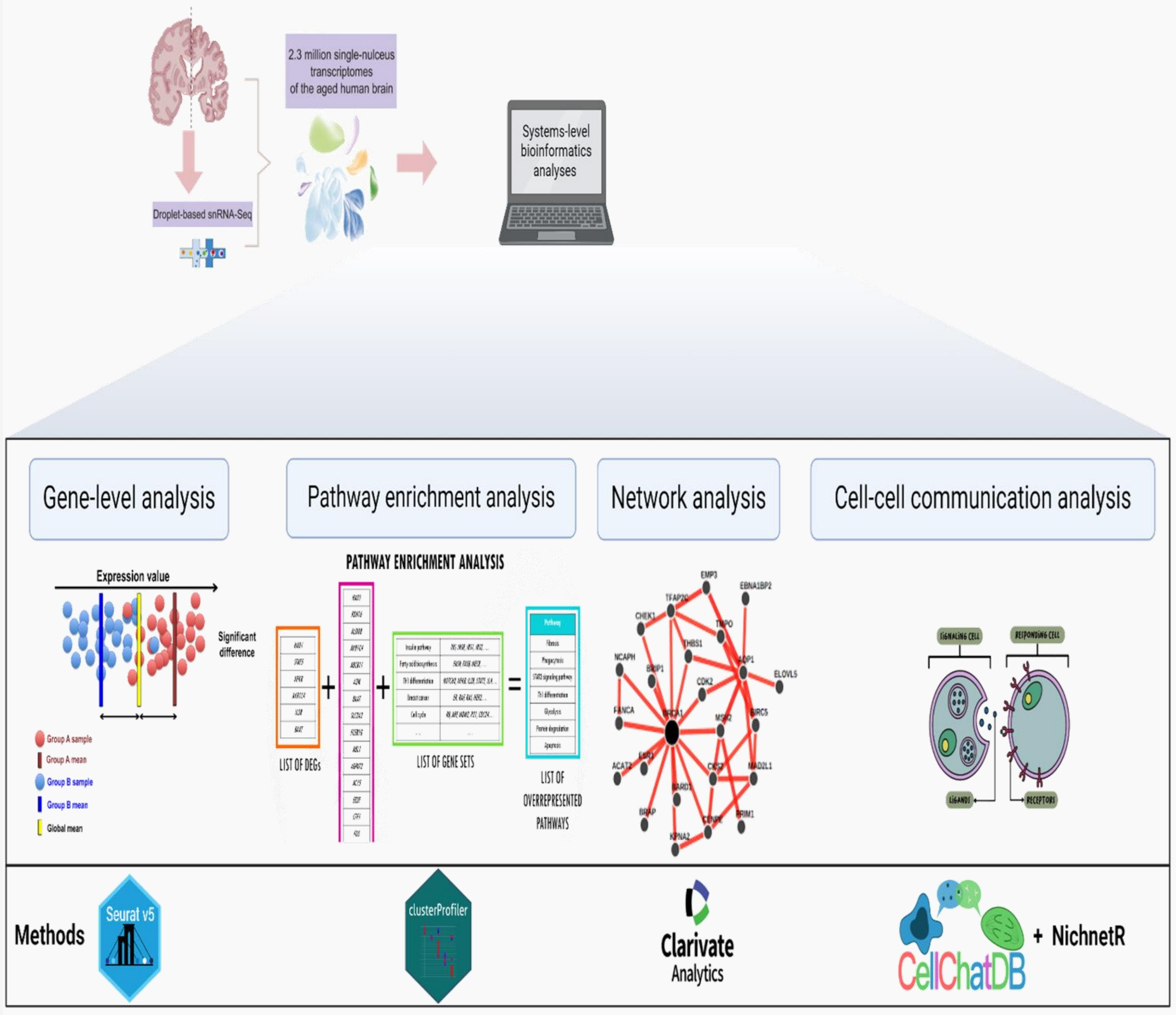
## Data



## Objectives

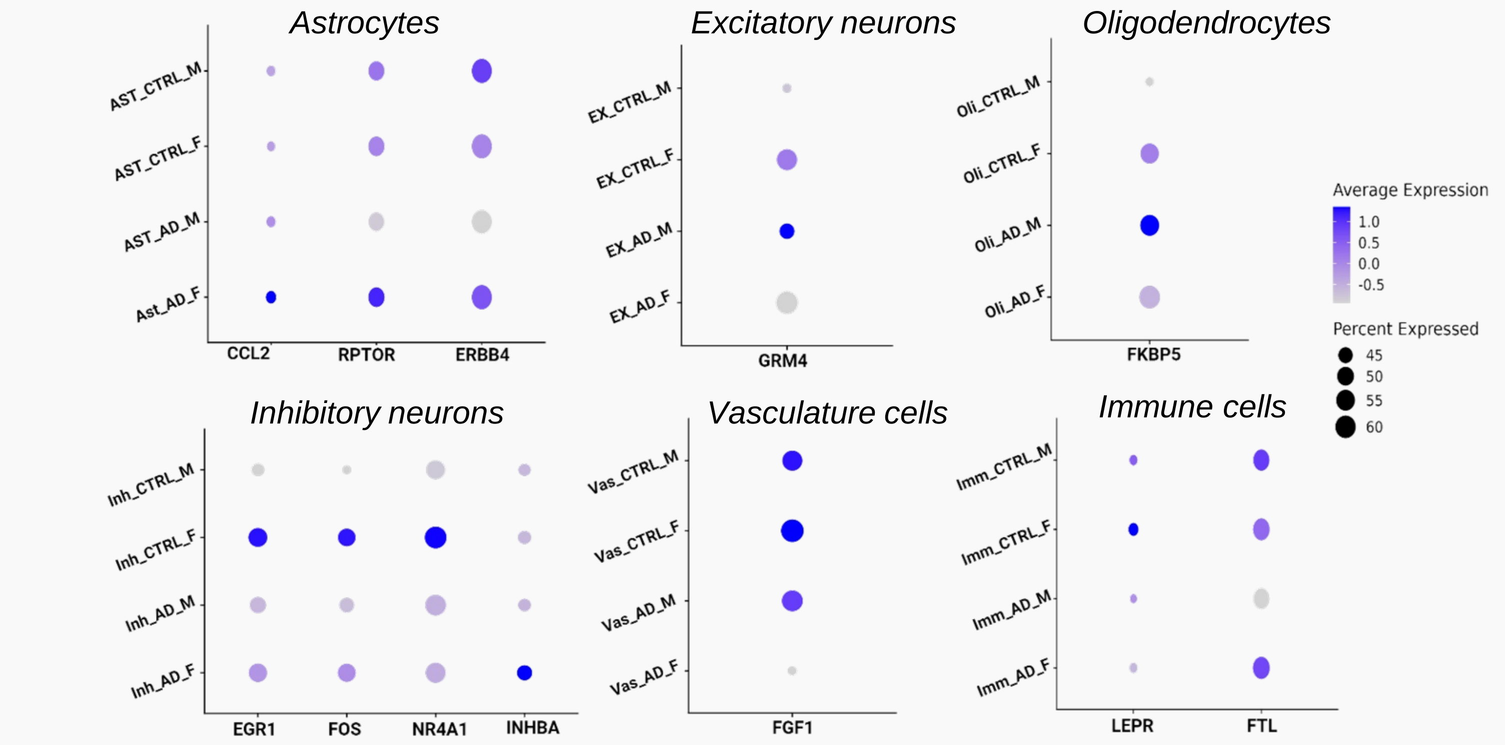
- Investigate the sex differences in AD by analyzing a large-scale single-cell transcriptomic atlas of the human prefrontal cortex.
- Conduct cell type-specific and sex-specific differential expression, pathway/network and cell-cell communication analyses to identify significant sex-dependent changes in AD.

## Methods

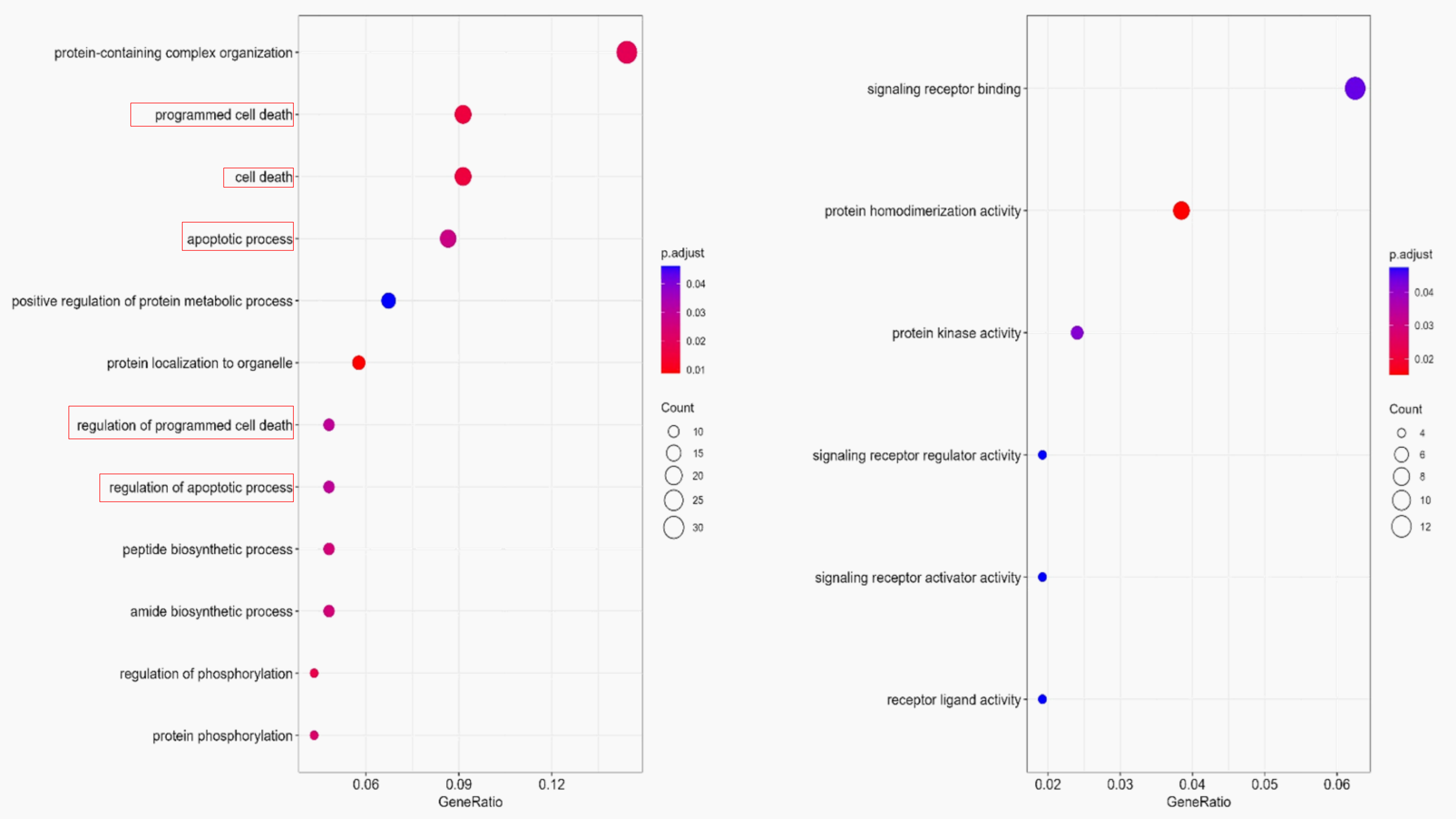

Droplet-based snRNA-Seq
2.3 million single-nucleus transcriptomes of the aged human brain
Systems-level bioinformatics analyses
Gene-level analysis
Pathway enrichment analysis
Network analysis
Cell-cell communication analysis
Expression value
Significant difference
PATHWAY ENRICHMENT ANALYSIS
LIST OF DEGs
LIST OF GENE SETS
LIST OF OVERREPRESENTED PATHWAYS
Methods
Seurat v5
clusterProfiler
Clarivate Analytics
CellChatDB
+ NichnetR

## Result

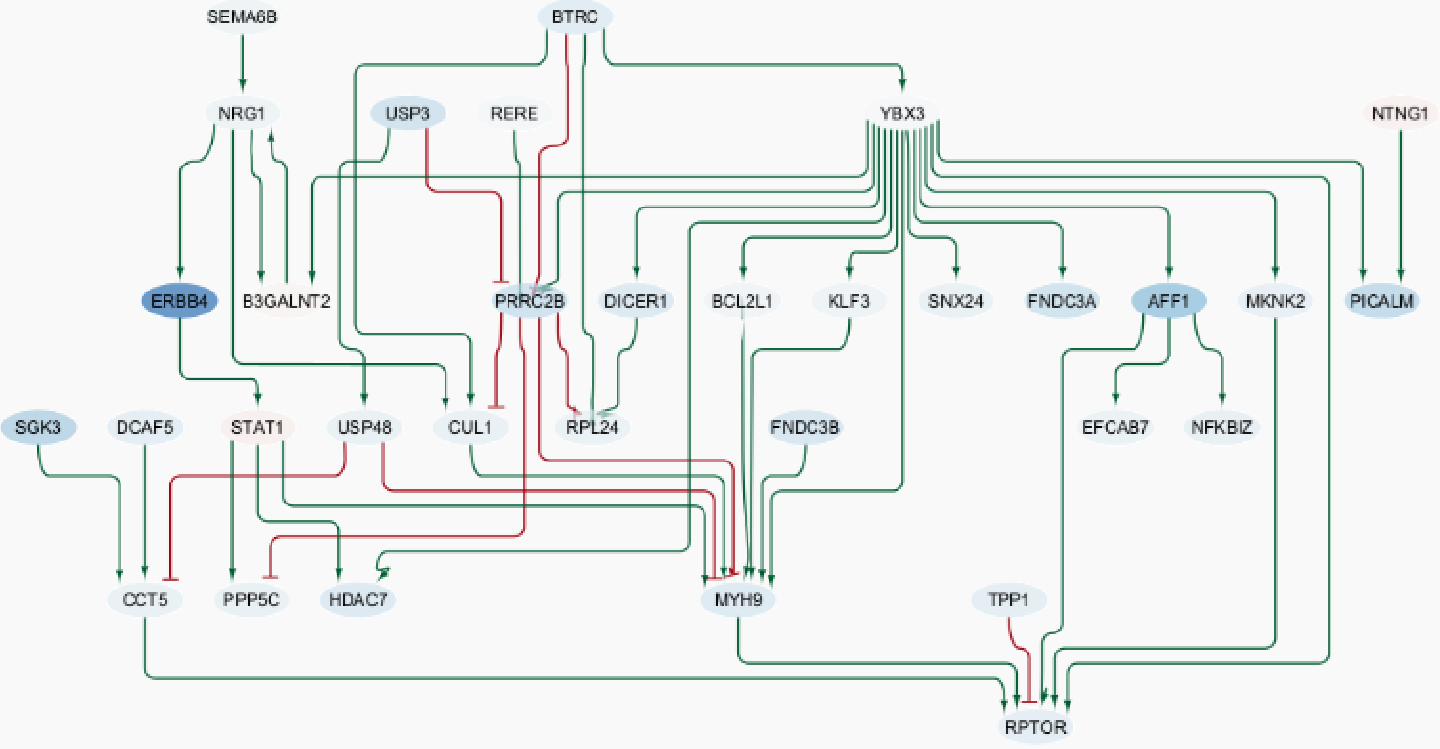
### Key differentially expressed genes across specific cell types in AD



### Enriched Gene Ontology (GO) terms in male astrocytes



### Graph representation of the GRN in astrocytes for male AD patients



## Conclusion

- Gene-level analysis revealed sex-specific DEGs in astrocytes, such as *ERBB4* and *SGK3* in males and *CCL2* and *INHBA* in females, highlighting the importance of considering sex-specific gene expression in understanding AD's molecular landscape.
- Pathway analysis detects sex-dependent differences in cellular responses to AD, with **males** showing changes in **apoptosis**, while **females** exhibit changes in **Wnt signaling**, **cell cycle**, and **calcium ion transport pathways.**
- Network and cell-cell communication analysis reveals sex-specific regulatory hubs, such as *NRG1* and *CCT5* in males and *LRP1* in females, alongside distinct intercellular signaling patterns involving **apoptosis** in **males** and **Wnt** and **calcium** pathways in **females**, suggesting differential contributions to AD progression.

[1] R. S. Wilson, E. Segawa, P. A. Boyle, S. E. Anagnos, L. P. Hizel, and D. A. Bennett, “The natural history of cognitive decline in Alzheimer’s disease,” Psychol. Aging, vol. 27, no. 4, pp. 1008–1017, Dec. 2012, doi: 10.1037/a0029857.

[2] A. Grubman et al., “A single-cell atlas of entorhinal cortex from individuals with Alzheimer’s disease reveals cell-type-specific gene expression regulation,” Nat. Neurosci., vol. 22, no. 12, pp. 2087–2097, Dec. 2019, doi: 10.1038/s41593-019-0539-4.

[3] Molecular characterization of selectively vulnerable neurons in Alzheimer’s Disease - PMC.” Accessed: Sep. 09, 2024. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7854528/